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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,101	MASS, ROBERT D.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 26-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/15/05, 5/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed March 27, 2006 in response to the Office Action of September 27, 2005, is acknowledged and has been entered. Claims 21 and 26-31 are pending and are currently being examined. There are no amendments to the claims.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained

Claim Rejections - 35 USC § 112

3. **Claims 21, 26-31 remain rejected under 35 U.S.C. 112, first paragraph,** because the specification, while being enabling for a method for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in breast cancer tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer, wherein the patient's tumor cells express HER2 at a **2+ or 3+** level by immunohistochemistry, does not reasonably provide enablement for a method for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer, wherein the patient's tumor cells express

HER2 at a **0 or 1+** level by immunohistochemistry. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims (see p. 2-5, section 4 of the Office Action of September 27, 2005).

The claims are drawn to a method for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, for treating breast cancer, comprising detecting her2 gene amplification and treating the patient with HER2 antibody, wherein the patient's tumor cells express HER2 at a 0 or 1+ level by immunohistochemistry.

The specification discloses the requirement for overexpression of HER2 at the 2+ or 3+ level immunohistochemistry (IHC) for enrollment in the Herceptin® breast cancer trials. The specification also discloses the detection of Fluorescence *In Situ* Hybridization (FISH) positive samples that were included in the Clinical Trials Assay (CTA) negative samples, samples that did not meet the 2+ or 3+ requirement (Example 1). The specification speculates that the identification of FISH+ patients in the 1+ and 0 sub-groups might identify subjects, though failing the IHC criteria for Herceptin® treatment, that would likely benefit from Herceptin® treatment. The specification further discloses a correlation between the FISH status with response to Herceptin® treatment for 2+ and 3+ subjects (Example2), wherein the FISH+ subjects showed a much greater response to chemotherapy and Herceptin® than FISH- subjects, suggesting FISH+ selection analysis in combination with IHC detection of HER2 overexpression provides a more accurate indicator of likelihood of success with Herceptin® treatment than for IHC

analysis alone (p. 32). The specification discloses that FISH identifies patients in the 1+ and 0 IHC categories who are excluded from treatment because expression of HER2 is too low for effective therapy (p. 32).

Other than a correlation between FISH+ subjects and 2+ and 3+ IHC subjects who responded favorably to treatment, there is only a hypothesis that 0 and 1+ patients would also benefit from treatment. One cannot extrapolate the teaching of the specification to the scope of the claims because, as drawn to the treatment of breast cancer that does not overexpress HER2, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen-negative cells can survive and repopulate a tumor (col. 1, line 64; col. 2, line 2). Further, Lewis et al (Cancer Immunology Immunotherapy 37: 255-263, 1993) specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in treating breast cancer that does not overexpress HER2. Successful, effective administration of HER2 antibody to treat breast cancer in 0 and 1+ IHC level patients cannot be predicted based only on the hypothesis provided by the specification. Low expression levels of HER2 at the 0 and 1+ IHC level in a breast cancer patient would suggest a lack of HER2 receptors present, and in the absence or near absence of receptor, it would not be expected that the antibody would be effective to treat,

especially in view of the teaching in the art that effective treatment would not be predictably expected at IHC levels less than 2+ or 3+.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

4. Applicants argue that the present invention enables the selection of all patients who are likely to benefit from HER2 antibody treatment and allows an early start to other treatments for patients who are not (p. 5, 1st para). Applicants argue that the present invention is from the field of antibody-based cancer therapy and it is well-established that the level of skill in the field is high. In view of the extensive teaching provided by the specification for the preparation of HER2 antibodies to treat breast cancer patients, detection of gene amplification and HER2 protein expression, and pharmaceutical compositions and methods of treatment, one of ordinary skill would know how to identify a patient whose tumor shows the specified characteristics and treat such a patient with a HER2 antibody huMAb4D5-8 (p. 5-6).

The argument has been considered but is not found persuasive. Applicants point to the lack of enablement determination using the *Wands* factors analysis. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court

in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not provide examples or guidance for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, for treating breast cancer, comprising detecting her2 gene amplification in tumor cells from the patient wherein the patient's tumor cells express HER2 at a 0 or 1+ level. The specification discloses a correlation between the FISH status with response to Herceptin® (huMAb4D5-8) treatment for **2+ and 3+** subjects (Example2), wherein the FISH+ subjects showed a much greater response to chemotherapy and Herceptin® than FISH- subjects, suggesting FISH+ selection analysis in combination with IHC detection of HER2 overexpression provides a more accurate indicator of likelihood of

success with Herceptin® treatment than for IHC analysis alone (p. 32). The specification speculates that the identification of FISH+ patients in the 1+ and 0 sub-groups might identify subjects, though failing the IHC criteria for Herceptin® treatment, that would likely benefit from Herceptin® treatment, however, 0 and 1+ patients were never treated with MAb4D5-8 because they did not meet the 2+ and 3+ level immunohistochemistry (IHC) requirement for enrollment in the Herceptin® breast cancer trials, hence, the predictive value of FISH+ and 1+ or 0+ results for identifying a patient disposed to respond favorably to MAb4D5-8 treatment is unknown and unsupported by the specification.

Further, the art teaches that low expression levels of HER2 at the 0 and 1+ IHC level in a breast cancer patient would suggest a lack of HER2 receptors present, and in the absence or near absence of receptor, it would not be expected that the antibody would be effective to treat, especially in view of the teaching in the art that effective treatment would not be predictably expected at IHC levels less than 2+ or 3+. As stated above in the rejection, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen-negative cells can survive and repopulate a tumor (col. 1, line 64; col. 2, line 2). Further, Lewis et al (Cancer Immunology Immunotherapy 37: 255-263, 1993) specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would

believe that it would be more likely than not that the invention would function as claimed in treating breast cancer that does not overexpress HER2.

The level of skill in the field of antibody-based cancer therapy is high, however, one of ordinary skill could not predict the favorable response of a patient that is FISH+ and has a 0 or 1+ IHC level to MAb4D5-8 treatment because the art teaches that antigen-negative cells do not respond favorable to antibody anti-tumor therapy (see above), those skilled in the art determined that HER2 overexpression at the 2+ or 3+ IHC level was required for enrollment in Herceptin® breast cancer trials, and the specification does not provide examples and guidance for identifying a patient disposed to respond favorably to Herceptin® (MAb4D5-8) treatment who's tumor cells express HER2 at a 0 or 1+ IHC level and has her2 gene amplification.

In view of the lack of guidance in the specification, the absence of working examples, the state of the art, and the quantity of experimentation necessary, it would require undue experimentation for one skilled in the art to practice the invention as claimed and claims 21, 26-31 remain rejected under 35 U.S.C. 112, first paragraph, as set forth above.

5. Applicants argue that low existing expression levels of HER2 in breast cancer patients (0 and 1+ IHC level) do not necessarily mean "a lack of HER2 receptor present" or "the absence or near absence of receptor", rather HER2 protein levels corresponding to a 0 or 1+ IHC score **might** just mean that the her2 and HER2 protein are present, but

the latter is not detected by IHC due to the limitations of IHC-based methods (p. 6, para 2).

The argument has been considered but is not found persuasive because Applicants are arguing limitations not recited in the claims. The claims are drawn to all patients that are her2 gene positive and have a HER2 0 or 1+ IHC level regardless of possible limitations and anomalies of IHC testing. Neither the specification nor the art provides examples or guidance supporting patients that are her2 gene positive and have a HER2 0 or 1+ IHC level would predictably respond favorably to MAb4D5-8 treatment. Low IHC levels of HER2 can include patients with little to no HER2 expression who would not respond favorably to Herceptin® (MAb4D5-8) treatment and it can include patients whose HER2 expression was inaccurately scored lower due to anomalies and flaws in laboratory testing. The specification and the art do not distinguish between these patients, hence one of skill in the art could not predict based on her2 gene amplification and a 0 or 1+ score if a patient would be disposed to respond favorably to Herceptin® (MAb4D5-8) treatment.

6. **Claim 31 remains rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method for identifying and treating a breast cancer patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with said HER2 antibody, does not reasonably provide enablement for a method for identifying and treating a patient disposed to respond favorably to HER2

antibody which inhibits cellular proliferation of HER2-overexpressing human breast tumor cells, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims (see p. 5-13, section 5 of the Office Action of September 27, 2005).

The claims are drawn to a method for identifying and treating a patient disposed to respond favorably to HER2 antibody which inhibits cellular proliferation of HER2-overexpressing human breast tumor cells, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer. This means the claims are drawn to a method of identifying and treating a patient comprising treating the patient with **any** HER2 antibody. This includes treating with (1) any antibody to HER2 regardless of where it binds on HER2, (2) regardless of whether it cross reacts with other antigens including EDGF receptor, (3) treating with polyclonal antibodies, (4) regardless of whether the antibody is humanized, and (5) regardless of the whether or not the carcinoma cells overexpress HER2 protein.

The specification discloses the successful treatment of cancer patients with HER2 antibody, huMAb4D5-8 or Herceptin® (p. 5, line 22).

One cannot extrapolate the teaching of the specification to the scope of the claims because (1) although the specification claims a method using any antibody to HER2, the specification specifically states that it is Herceptin®, and not any HER2 antibody, which is postulated as a therapeutic strategy for cancer patients with breast

cancer overexpressing HER2 (p. 16, lines 3-10). It is clear that it is well known in the art Herceptin® is an effective anti-cancer agent in tumors that overexpress HER2. However, other than stating that this well-known antibody, Herceptin®, is an example of the claimed antibodies of the invention, the specification does not teach how to make a therapeutic antibody with the properties required for effective treatment of HER2-overexpressing breast cancer so that it will function as claimed. For example, Stancovski, et al (PNAS,USA, 88:8691-8695, 1991) characterized the effects of various antibodies that bind the extracellular domain of ErbB2 upon the growth of tumor cells. Stancovski, et al teach, while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth (page 8693, column 1). This phenomenon was also reported in Lewis, et al (Cancer Immunology Immunotherapy 37: 255-263, 1993). US Patent No. 5,677,171 teaches that not every anti-ErbB2 antibody can be used as effectively as monoclonal antibody 4D5 (col 18, lines 15-23). More specifically, '171 teaches that some anti-ErbB-2 antibodies inhibited growth to a lesser extent than MAb 4D5 while others failed to inhibit growth. Further, Strobel, et al (Gynecologic Oncology 73: 362-367, 1999) teach discordant effects of contacting cancer cells with two different neutralizing monoclonal antibodies, i.e., antibodies that block the function of the receptor protein to which they specifically bind (abstract). Despite the fact that both anti-receptor antibodies had been shown to block ligand binding to the receptor, Strobel et al found that only one of the antibodies could be used effectively to block cancer cell adhesion to inhibit malignancy. Thus, in the

absence of guidance on how to make effective antibodies, other than huMAb4D5-8, one could not predictably practice the broadly claimed invention.

Further, clearly one would not expect to be able to practice the claimed invention with an antibody that was not specific for the extracellular domain of HER2, for example an antibody to the intracellular domain or an antibody that binds only to denatured HER2, because the antibody would not bind to malignant cells expressing ErbB-2, since the antibody could not contact the intracellular domain of the protein, would not be able to bind to a folded protein and therefore would not inhibit the cells growth and/or proliferation. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (2) cross-reactivity of the broadly claimed antibody. It is well known in the art, as taught by Karunagaran et al (EMBO J., 1996, 15:254-264) and Graus-Porta et al (EMBO J., 1997, 16:1647-1655), that HER2 is a member of the EGFR family and shares homology with other members of the family. Given the shared homology it would be expected that antibodies that are not selective for HER2 would cross react with, and be sequestered by, other members of the EGFR family. In particular it is known that anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of

time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the anti-tumor antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (3) polyclonal antibodies. The claim as written read on monoclonal and polyclonal antibodies. As set forth above, given the identity of HER2 with other members of the EGFR family, it would be expected that a large majority of polyclonal antibodies would bind to epitopes that are shared among members of the EGFR family. These sequestered antibodies would not be available to treat the cancer and it could not be predicted, for the reasons set forth above that the broadly claimed method will function as claimed with a reasonable expectation of success using polyclonal antibodies.

As drawn to (4) non-humanized antibodies, Winter et al (TIPS, 1993, 14:139-143) specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of human antimouse antibodies (HAMA) that can inactivate the injected antibodies. Thus, it would be expected that the injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. Further, Baselga et al (J. Clin. Oncol, 1996, 14:737-744) specifically teach that murine antibodies are limited clinically because they are immunogenic. To facilitate clinical investigations, MAb 4D5 (the murine parent antibody of HERCEPTIN) was humanized. The humanization resulted in a safe treatment which has dose dependent pharmacokinetics in phase I clinical trials (p. 737, col 2). Given the teaching in the art, it could not be predicted and it would not be expected that non-humanized antibodies would function as claimed, that is as a therapeutic for the treatment of HER2-overexpressing breast cancer patients that is clearly contemplated.

As drawn to (5), treatment of cancer that does not overexpress HER2 protein, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen negative cells can survive and repopulate a tumor (col 1, line 64, col 2, line 2). Further Lewis et al, Supra, specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed

in a cancer that does not overexpress HER2. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

7. Applicants did not address the rejection of claim 31 under 35 U.S.C. 112, first paragraph (above).

8. Applicants argue a rejection of claims 1,2,3,5,6,7,8,and 12 under 35 USC 103 (see p. 7-10), however Examiner never rejected claims 1,2,3,5,6,7,8,and 12 under 35 USC 103 in the Office Action of September 27, 2005 and, more importantly, claims 1,2,3,5,6,7,8,and 12 are not part of the elected invention. Claims 21 and 26-31 are currently being examined. Hence, the arguments are irrelevant to the claimed invention.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED

STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER